

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	Oleg Illich Epshtein	Confirmation No:	4128
Application No:	09/117,838	Group:	1623
Filed:	August 12, 1998	Examiner:	Peselev, Elli
For:	Medicinal Preparation and a Method of Medicinal Action on Human Organism		
Customer No.:	29127		
Attorney Docket No.	0075.0006US1		

DECLARATION UNDER 37 C.F.R. § 132 OF
INVENTOR OLEG I. EPSHTEIN

1. I am Oleg I. Epshtein, a named inventor in the above-referenced U.S. patent application. I declare and affirm under the penalty of perjury under the laws of the United States that the following is true and correct based on my personal knowledge, or where not on my personal knowledge, on my information and belief.
2. I am the principal of the company "Materia Medica" which has been closely involved in the development and testing of the invention claimed in the referenced U.S. patent application. I declare as follows:
3. Homeopathic therapy and technique have been known and used since about two centuries ago. Homeopathic treatment has been founded on the principle of individualization of compounds with therapeutic activity used in ultra low doses.
4. About 20 years ago modern experimental research has shown that, independently of being tied to a specific scientific theory or explanation, ultra low doses of such compounds exhibit biological activity. It has been suggested that the observed biological activity is the result of method of preparation of the solutions: a combination of multiple consecutive dilutions and the influence of mechanical factors, all together known as a homeopathic potentiation technology. If other techniques of preparing ultra-diluted solutions are used, such as, for example, medical micropipetting, ultra diluted solutions did not exhibit biological activity.

5. The following is the results of my experimental and clinical studies of the bipathy phenomenon. The essence of bipathy phenomenon is in the modification effect of the ultra low doses (ULD) of a biologically active compound on the same compound when they are administered together (combined administration).
6. Prednisolone, a glucocorticoid anti-inflammatory drug, was first used to demonstrate bipathy phenomenon. In the model of carrageenan-induced inflammation isolated administration of an ultra low dose of prednisolone (C30) only did not demonstrate a significant anti-inflammatory effect; however, combined administration with prednisolone (20 mg/rat) resulted in the enhancement of an anti-inflammatory effect of the drug (for example, the migration ability of the peritoneal macrophages has increased 1.8 times ($p < 0.05$), the biosynthetic activity of lymphocytes was stimulated by 43.5 %, $p < 0.05$), as well as in the reduction of the prednisolone (at doses of 20 mg/ kg and 50 mg/ kg) side effects after 2- week administration (preventing destructive changes in liver, adrenal glands, lymph nodes, gastric erosion, peripheral blood changes, disturbance of cellular metabolism in lymphocytes and neutrophils).
7. The ultra low dose of prednisolone (C12+C30+C200) enhanced the analgetic potency of prednisolone at a dose of 53 mg/ kg in the model of acetic acid-induced writhing. The combined administration of prednisolone and ultra low dose of prednisolone caused the reduction in the number of writhings by 30.6% ($p < 0.05$) and in the pain sensitivity (% from the control) – by 26.4 % ($p < 0.05$) as compared to an isolated administration of prednisolone.
8. The fundamental physicochemical characteristics of the bipathy phenomenon were shown when an ultra low dose (C30) of the adenosine triphosphoric acid (ATP) was added to the solution containing an ATP disodium salt, citric acid monohydrate, sodium hydroxide, deuterio- hydrogen – D2 (99.9%), distilled water, ATP hydrolysis (measured by Furier spectrometer NMR Varian Unity 300) slowed down by 12.5 % ($p < 0.05$) as compared to the solution not containing ULD ATP.
9. Alternating current inversion voltammetry was used to measure characteristics of inversion voltammetric signals in the reaction of oxidation and reduction of mercury ions in the presence of potentiated water, potentiated lithium chloride and potentiated mercury nitrate. Intensification of mercury reduction and decrease in electrochemical reciprocity of mercury dissolving was observed in the presence of potentiated mercury nitrate; it was manifested in high rates of signal magnitude and peak broadening (52-87 mV). Enhancement of mercury activity was more pronounced in the presence of potentiated mercury nitrate than in the presence of potentiated water (44- 71 mV) and lithium chloride (34- 53 mV). The data proved that potentiated substances are able to modify specifically kinetic and thermodynamic characteristics of the same compounds solutions.
10. The bipathy phenomenon was also confirmed at the molecular level - the ability of ultra low doses of antibodies to influence antigen-antibody reaction was demonstrated in 2003. Two independent studies (conducted with use of ELISA assay) confirmed that the ultra low doses of antibodies altered the antigen- antibody binding constant. Thus, it

was shown that an ultra low dose of anti- morphine reduced the affinity binding of the anti-morphine antibodies to morphine (at C50 and C 200 dilution the reduction exceeded 80%). Ultra low doses of a delta sleep-inducing peptide (DSIP) (C 50 and C200) reduced the anti- DSIP antibodies affinity to DSIP by 30 % at average.

11. Bipathy effect was confirmed both in experiments (*in vitro* and *in vivo*) and in clinical trials.

12. *In vitro* experiments used the model of long-term potentiation (LTP) in hippocampus slices. The experiments showed that ultra low doses of the antibodies to S100 protein (ultra low doses of anti-S100) eliminated the inhibiting effect of a physiological concentration of antibodies to the S100 protein. Incubation of the hippocampus slices in the medium containing antibodies to the S100 protein resulted in a complete blocking of LTP. Preincubation of the hippocampus slices with ultra low doses of anti-S100 (C50 and C 200) diminished the inhibiting effect of the antibodies to S100 protein on LTP.

13. *In vivo* experiments used such substances as ethanol, morphine, cyclophosphane, phenazepam to show the bipathy effect.

14. Ultra low doses of ethanol (C30 and C200, per os) administered in combination with a 5 % ethanol solution (1.5-2.0 g/ kg) inhibited eliminating ethanol from blood, and also inhibited augmenting liver alcohol dehydrogenase activity in rats . The fourteen-day and four-month combined administration of ethanol combined with the ultra low doses of ethanol (C200) showed a considerable increase of the concentration of ethanol in blood (2- fold; $p<0.05$) and a sizeable increase in the activity of the liver alcohol dehydrogenase as compared to an isolated ethanol administration.

15. A study of the concentration of biogenic amines in the hypothalamus and cerebral septum in rats demonstrated that a single administration of an ultra low dose of ethanol inhibited the ethanol- induced reduction of dopamine (by 62%) and the adrenaline levels (by 45%, $p<0.05$), as well as increased the noradrenaline (by 85%, $p<0.05$) and serotonin levels (by 48%, $p<0.05$). A single and course administration of an ultra low dose of ethanol (C200) in combination with ethanol inhibited the decrease of the serotonin concentration in the hypothalamus and septum in rats (the neuro- mediator concentration was significantly higher (by 32%, $p<0.05$) for the bipathy administration as compared to an isolated ethanol administration).

16. The peripheral effects differed from the central effects, such that the bipathy administration of an ultra low dose of ethanol inhibited an increase in blood catecholamines in rats as compared to the group receiving the ethanol alone. This fact has confirmed that ethanol inhibits sympathoadrenal system activation.

17. Combined administration of an ultra low dose of morphine and 1% solution of morphine hydrochloride at a dose of 1 mg/kg for 10 days reduced pain sensitivity threshold as compared to isolated morphine administration.

18. Administration of an ultra low dose of morphine (0.1 ml/kg) under morphine-deprived condition to morphine-addicted rats reduced self-stimulation frequency by 21% ($p<0.05$) thus reflecting restoration of positive reward stimulation. Single and course administration of an ultra low dose of anti-morphine on the background of abstinence reduced active avoidance response, increased freezing response to sound irritant; reduced the intensity of startle response (in 4, 8 times) and decreased latency of tail flick procedure in the pain sensitivity test (in 2 times, $p<0.05$). Thus administration of ultra low doses of morphine under abstinence syndrome in rats increases functional activity of positive reward stimulation.

19. Two experimental tumor models (Lewis lung carcinoma and Walker carcinosarcoma 256) were used to show bipathy effect of cyclophosphane. The model of Lewis lung carcinoma (tumor cells were transplanted into mice intramuscularly in the hind thigh, 4×10^6 cells) was used to show that simultaneous intra abdominal administration of cyclophosphane both in therapeutic (125 mg/kg) and an ultra low dose (C12+C30+C200) caused augmentation of cyclophosphane antimetastatic action; the number of metastases on cyclophosphane administration decreased in 2 times ($p<0.05$), and inhibition index increased by 13% as compared to isolated administration. It should be noted that bipathy effects of cyclophosphane retained on peroral administration of an ultra low dose of cyclophosphane. In such case frequency of metastasis reduces by 39% ($p<0.05$), and the number of metastases decreases in 3 times ($p<0.05$) as compared to isolated cyclophosphane administration.

20. Walker carcinosarcoma 256 model (tumor cells were transplanted into mice subcutaneously in 0.2 ml of 20% salt solution) was used to show that 3 times bipathy administration of cyclophosphane with 48 hour intervals (simultaneous intra abdominal cyclophosphane administration at a dose of 20 mg/kg and intragastrical cyclophosphane administration at C12+C30+C200 dilutions) resulted in 2-fold reduction of tumor mass ($p<0.05$); the number of animals with metastases decreased by 13% as compared to isolated cyclophosphane administration using the same scheme.

21. Phenazepam is benzodiazepine anxiolytic and possess anxiolytic, anticonvulsive, sedative, muscle relaxant and soporific effect. Ultra low doses of phenazepam (C12+ C30 +C200, 2.5 ml/kg, i.g) considerably enhanced anxiolytic and anticonvulsive effect of therapeutic dose of phenazepam (1 mg/kg, i.g) at simultaneous administration. In Vogel Conflict test the number of punished water intakes (that are considered to be characteristic of anxiolytic effect of the drug) on simultaneous administration of both phenazepam and an ultra low dose of phenazepam increased in 3.6 times ($p<0.05$) as compared to the isolated administration of phenazepam. In pentylenetetrazol test simultaneous administration of phenazepam both in ultra low and therapeutic doses significantly increased anticonvulsive effect of phenazepam; it resulted in 2-fold increase in latency periods of convulsions seizure ($p<0.05$), decrease in percentage of animals with convulsions (by 60%, $p<0.05$), and survival rate increase (by 60 %, $p<0.05$). Combination of an ultra low dose and therapeutic doses of phenazepam inhibited development of phenazepam-related side effects (as anxiolytic of benzodiazepine family)

– sedation and muscle relaxation. At that specific activity of an ultra low dose of phenazepam was detected. It was shown that an ultra low dose of phenazepam enhance only specific effects of phenazepam, but did not influence cataleptogenic action of haloperidol and antidepressant effect of amitriptylin on combined administration of an ultra low dose of phenazepam with these drugs.

22. I present the following results of the clinical trials on the bipathy phenomenon:

23. 370 patients of both genders (aged 18-60) with stage II chronic alcoholism not accompanied by acute concomitant somatic and mental disorders were enrolled in the “Anti- E” clinical trials, permitted by Ministry of Health of Russian Federation. Included in the study were the subjects were hospitalized immediately after the end of a drinking bout or during a drinking bout.

24. The subjects were randomized into Anti – E groups (within the first 48 hours the subjects received 8-10 drops per tablespoon of water at 1-h intervals with time for a sleep break and 5 times a day (day 3 of the trial) as monotherapy (n=132) or in combination with the detoxication therapy (n=67). The subjects of the control group (n=171) received standard detoxication drugs (intramuscular injections of vitamins B1 and B6, intravenous infusions of 30 % sodium thiosuphate, 4 % glucose solution, vitamin C); if required sedative drugs were used.

25. Psychopathological, neurological and somatovegetative characteristics, as well as side effects caused by the drug administration, were recorded to assess the efficacy and safety of the therapy.

26. In the “Anti- 13” clinical trial, permitted by Ministry of Health of Russian Federation, 144 patients with opium withdrawal syndrome (OWS) on the background of opiumism were enrolled in the study. Patients undergoing both hospital and outpatient treatment without neurological, somatic and mental disorders not induced by opium addiction were included in the study. The included patients were divided into 2 groups - Anti- 13 group as monotherapy (7-15 drops per soup spoon of water at 1-h intervals first 2 days of treatment; and 5 – 8 times a day on days 3-5) (n=80), in combined therapy with bioresonance therapy, Clophelin, Tiapril, Tramal (n=34). The patients receiving monotherapy could be treated with benzopiazepine hypnotics to relieve insomnia disorder. The patients of comparative group (n=30) received Clophelin, Tiapril, Tramal.

27. The patients’ state was assessed daily by evaluation of severity of OWS psychopathological, neurological and somatovegetative symptoms by an adapted 5-point Himmelsbach scale. The efficacy of treatment was determined by total severity of withdrawal symptoms and subjective evaluation of patients. For standardization we used report forms where patient data, information of severity of AWS and OWS symptoms as well as adverse events induced by the drug administration were recorded.

28. Results. Demographic data and severity of basic disease were equal in the study groups (Table 1).

Table 1. Average anamnestic parameters in patients with AWS

Parameter	Main group (n=199)	Control group (n=171)
Age (years)	41.7±1.6	39.3±1.4
The duration of drinking bout	13.3±1.23	11.7±1.4
The duration of hang- over (years)	9.5±1.1	7.7±0.8
The duration of drinking bout during hangover (days)	7.5±0.85	8.3±0.9
Average daily dose of alcohol during drinking bout (liters)	0.85±0.06	0.75±0.09
Initial intensity of symptoms in patients (total score)	23.2 ±0.8	21.1±0.1

29. Initially the average severity of the patients' state with AWS in both groups exceeded 20 points. The most significant difference in severity of symptoms was observed on days 2 and 3; thus indicating that Anti- E posses selective activity; it is able to reveal rapidly acute AWS symptoms; that it is more potent than disintoxication therapy. By days 4 and 5 these differences disappeared.

30. In Anti-E group significant reduction in neurological disturbances (tremor - from 4.8±0.6 to 2.6±0.3 (days)); ataxy – from 3.8±0.5 to 2.2±0.2 (days)), thirst (from 2.9±0,3 to 1.5±0,1 (days)) and sweating (from 3.1±0.3 to 1.8±0.2 (days)); besides reduction in intrasomnic disorders frequency was observed. However, the duration of arterial hypertension in the main group was significantly higher than in comparative group (2.7±0. and 1.6±0.2 days respectively).

31. In most patients's clinical data in general coincided with the patients' subjective evaluation. In half of patients drug administration decreased the severity of weakness and discomfort; the drug improved sleep in 10% of patients. In some subjects the drug selectively influenced gastritis- like symptoms, improved sleep and quickly relieved asthenia symptoms. Considerable effect of the drug on anxious-depressive symptoms, alcohol addiction and other psychopathological disturbances was not registered. The use of Anti – E as monotherapy significantly reduced the duration of AWS relieve (Figure 1)

32. Figure1. Dynamics of general AWS severity induced by Anti- E therapy

Dynamics of general AWS severity

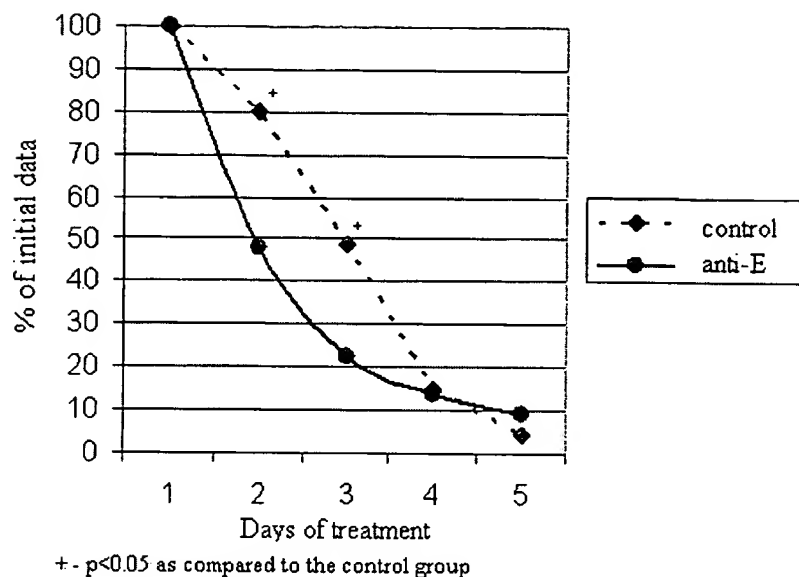


Table 2. Severity of symptoms in patients with AWS and OWS (total score)

Follow-up period (days)	AWS				OWS	
	Control (n=171)		"Anti-E" (n=199)		Control (n=30)	"Anti-13" (n=114)
	Abs	%	Abs	%		
1	21.1±0.1		23.2±0.8		28.7±0.9	26.8±1.1
2	16.9	80.1	11.2	48.3*	20.3±1.1	19.7±1.1
3	10,3	48,3	5,3	22.8*	18.5±0.8	18.4±1.5
4	3.2	15.2	3.16	13.6	5.3±0.51	4.8±0.5
5	1.0	4.7	2.1	9.1	2.3±0.31	2.4±0.36

* - p<0,05 as compared to control

33. The analysis of Anti – E efficacy in relieve of AWS symptoms was conducted in the subjects' group with comorbid traumatic cerebral injury. The drug (n=30) or placebo (n=30) were administered on the background of a basic AWS therapy (hemodez, isotonic solution of sodium chloride, the B group vitamins, ascorbic acid, butiroksan, sodium thiosulfate, tranquilizers, nootropics, vascular drugs) in accordance with the following treatment regime: within the first 48 hours 3-5 drops every hour then 5 times a day for 10 days.

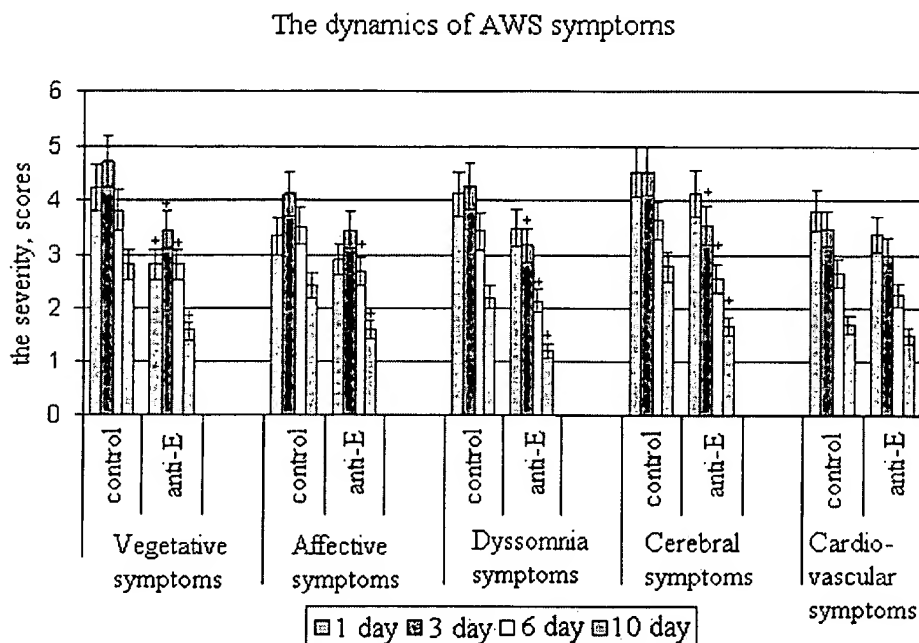
34. The use of Anti-E on the background of a traditional detoxification therapy

considerably reduced the severity of majority of AWS symptoms (Figure2). Dysomnia and affective symptoms of the syndrome were treated by the drug most effectively; rapid reduction of asthenic disorders was observed.

35. Thus clinical study of Anti- E (as relieving acute AWS symptoms drug) showed certain advantages of this drug in comparison with the basic therapy. Hypnogenic activity of the drug; its positive effect on neurological disorders, vegetative disturbances and gastric dyspepsia were observed. Having no considerable effect on anxious-depressive disorders, alcohol addiction and other psychopathological disturbances, Anti – E produced a moderate effect on asthenodynamic and astheno- depressive disorders in patients with acute AWS.

36. Anti- E did not cause considerable side effects. In patients with acute AWS only an increase in the duration of arterial hypertension was observed (i.e. no more than 3 days). Anti-13 was effective in 36% of patents with AWS. It produced the therapeutic effect immediately after its administration; it was manifested by reduction of anxiety, trouble, the feeling of general weakness. The severity of sweating, chill, sneezing, watery eyes, salivation as well as pulling muscle pains reduced; appetite was improved. However, the drug had no effect on nausea, dyspepsia and vomiting. Besides, all the patients required additional hypnotic treatment because of sustained insomnia.

37. **Figure 2.** The dynamics of AWS symptoms on the background of Anti- E therapy in patients with comorbid traumatic cerebral injury



+ - $p < 0,05$ as compared to the control group

38. **Table 3.** The duration (days) of fundamental symptoms of OWS in subjects of the main and control groups.

Symptom	Control	Anti-13
Yawning	1.3±0.1	1.7±0.14
Watery eyes	2.2±0.23	1.4±0.14***
Salivation	1.2±0.2	1.4±0.15
Sneezing	2.1±0.2	1.4±0.11***
Sweating	2.6±0.27	1.7±0.11***
Tremor	2.5±0.19	1.5±0.12*
Chill	3.2±0.22	2.3±0.14**
“Gooseflesh”	1.5±0.13	1.4±0.1
Anxiety and restlessness	3.4±0.43	2.3±0.1
Pain in muscles and joints	3.5±0.33	2.7±0.13
Mydriasis	2.7±0.3	2.5±0.13
Dyspnea	1.1±0.12	1.2±0.1
Arterial hypertension	1.2±0.18	1.6±0.12
Tachycardia	3.3±0.34	2.4±0.11***
Drug addiction	3.2±0.32	2.54±0.2

* - $p < 0,05$; ** - $p < 0,01$; *** - $p < 0,001$

39. Anti-13 more rapidly relieved vegetative and neurological symptoms of acute OWS than the standard therapy (Table 3); positive anxiolytic, muscle relaxant and analgetic effect of the drug were registered. The duration of other OWS symptoms did not differ in all groups (Table 2). In 5-10 minutes after Anti-13 administration the majority of patients (84%) had a feeling of mild euphoria, general relaxation, tongue numbness; at that disarthria, mild stammering, the changes of timbre were observed objectively.

40. As monotherapy Anti- E and Anti-13 could be used to treat light and mild AWS and OW; in combined therapy the drug could be used to relieve more severe OWS symptoms and AWS with comorbid traumatic cerebral injury. Drug doses and duration of the treatment course are determined individually based on the severity of AWS and OWS symptoms.

41. Thus bipathy phenomenon was shown in experimental studies in examples of different biologically active compounds and was proved in clinical studies.



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